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09/965,116	09/26/2001	Ekambar R. Kandimalla	HYZ-479CP (47508.577)	3956

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 07/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/965,116	KANDIMALLA ET AL.	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/09/03, 1/23/04, and 06/01/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *9-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/17/01, 02/01/02, 10/15/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Art Unit Location

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1648, Examiner Emily Le.

Amendments Received

2. The Examiner has considered the following amendment(s) and/or Applicant filed response(s): 10/09/03, 1/23/04, and 06/01/04.

Election/Restrictions

3. Applicant's election without traverse of Group I, claims 1-8 in the reply filed on 10/09/03 is acknowledged.

4. Claims 9-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/09/03.

Status of Claims

5. Claims 1-38 are pending in the instant application. Claims 1-8 are drawn to the elected invention. Claims 9-38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10/09/03. Claims 1-8 are currently under examination.

Specification

6. Applicant is reminded to update the status of all priority documents that is disclosed on the first full paragraph of page 1 in the specification.

7. The drawings that are included in the instant application is objected to for the following informalities, for example: i) the notation used to identify each oligonucleotide compounds in Figure 25A is not consistent with those used in Figure 25B. The same is true for Figure 26.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 3-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites a dependency to "claim 0". No such claim, claim 0, exists in the instant application. Therefore, it is unclear what is the dependency of claims 3 and 4-8--which depends on claim 3.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for immunostimulating oligonucleotides that comprises a minimum of 5 oligonucleotides and wherein the oligonucleotides must

follow the following motifs: i) follows the formula: 5'TCGXX-3'[1], wherein the C is a non-natural pyrimidine, G is a natural and/or non-natural purine group, and X is any nucleotide; ii) contain two purine bases on the 5' side and two pyrimidine bases on the 3' side of the CpG motif, such as GACGTT; and iii) contain the palindromic 'AACGTT' residue[2]. The specification does not reasonably provide enablement for immunostimulatory sequences that are shorter than 5 nucleotides in length and that does not follow the above motifs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex*

[1] Fearon et al. A minimal human immunostimulatory CpG motif that potently induces IFN-gamma and IFN-alpha production. Eur. J. Immunol. 2003, Vol. 33, pages 2114-2122, see abstract.

[2] Kandimalla et al. Toll-like receptor 9: modulation of recognition and cytokine induction by novel synthetic CpG DNAs. Biochemical Society Transaction, 2003, Volume 31, part 3, pages 654-658, see bridging paragraph on page 654.

parte Forman [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to oligonucleotide compounds that comprise the following motif CpG, wherein the C is a non-natural pyrimidine, G is a natural and/or non-natural purine group. The claims further require that the oligonucleotide compounds be immunostimulating.

Currently as written, the breadth of the claims encompasses all oligonucleotide compounds that are i) immunostimulating and ii) contain the following motif: CpG, wherein the C is a non-natural pyrimidine, G is a natural and/or non-natural purine group; wherein the length of the oligonucleotide compounds can be as short as 2 nucleotide residues, wherein the residues are C and G-- wherein the C is a non-natural pyrimidine, G is a natural and/or non-natural purine group. Because of the breadth of the claims reads on oligonucleotides that can be as short as 2 residues long, it is contemplated that one skilled in the art cannot practice the full scope of the claimed invention without an undue burden of experimentation. This assertion is made on the basis of the teachings of Fearon et al. Fearon et al. teaches that there is a minimal number of nucleotide resides that is required for an oligonucleotide that comprises the natural bases of cytosine and guanine in the CpG motif is 5. This minimal number of

nucleotide resides is necessary for oligonucleotides that comprises the CpG motif to induce an immune response. While it is acknowledge that the teaching of Fearon et al. is directed to natural nucleotide residues, however, the teaching of Fearon et al. is considered relevant to the instantly claimed invention. This is so because both the Fearon et al. and the instantly claimed invention is directed at oligonucleotides that are immunostimulating and shares a common motif, CpG.

Because Fearon et al. teaches that there is a minimal number of residues that is required of oligonucleotides that comprise the CpG motif, one skilled in the art would not be able to practice the full scope, which includes oligonucleotides that are shorter than 5 nucleotide residues in length, the claimed invention without an undue burden of experimentation. Furthermore, in conjunction with the required minimal number of nucleotide residues for the oligonucleotide to be immunostimulating, one of ordinary skill in the art would not be able to practice the instantly claimed without an undue burden of experimentation unless the oligonucleotide specifically have the following i) the formula: 5'TCGXX-3', [3] wherein the C is a non-natural pyrimidine, G is a natural and/or non-natural purine group, and X is any nucleotide; ii) contain two purine bases on the 5' side and two pyrimidine bases on the 3' side of the CpG motif, such as GACGTT; or iii) contain the palindromic 'AACGTT' residue[4]. This is so because Fearon et al. and Kandimalla et al. teaches that only oligonucleotides that comprises those specific residues stimulate an immune response in mice and/or human.

[3] Fearon et al. A minimal human immunostimulatory CpG motif that potently induces IFN-gamma and IFN-alpha production. Eur. J. Immunol. 2003, Vol. 33, pages 2114-2122, see abstract.

Additionally, the disclosure in the specification does not further aide the skilled artisan to practice the claimed invention without an undue burden of experimentation. The specification contains teachings that are directed at oligonucleotides that are of primarily 18 nucleotide residues in length. The specification does not contain any teachings that is directed at oligonucleotides that are immunostimulating that are less than or greater than 18 nucleotide residues in length.

Therefore, in view of the i) lack of guidance that is provided in the specification, ii) high level of unpredictability in the art, as exemplified by Fearon et al., iii) the state of the art; it is concluded that one skilled in the art would not be able to practice the full scope of the instantly claimed invention without an undue burden of experimentation.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

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[4] Kandimalla et al. Toll-like receptor 9: modulation of recognition and cytokine induction by novel synthetic CpG DNAs. Biochemical Society Transaction, 2003, Volume 31, part 3, pages 654-658, see bridging paragraph on page 654.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Krieg et al.

The claim is directed an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural or non-natural purine nucleoside. The claimed compound is also defined as C*pG, wherein C* is a cytidine analog, G is guanosine, 2'-deoxyguanosine, or a guanosine analog, and p is an internucleotide linkage selected from a group consisting of phosphodiester, phosphorothioate, and phosphorodithioate. The claims further require that the 5th position, which is a carbon, in the non-natural pyrimidine linked to a side group selected from the group consisting of hydrogen, hydrogen bond donor, hydrogen bond acceptor, hydrophilic group, hydrophobic group, electron withdrawing group and electron donating group, and the 4th position, which is a carbon, in the non-natural pyrimidine linked to a side group a hydrogen bond donor. The claim further requires that the 3rd position in the non-natural pyrimidine to be a hydrogen bond acceptor or a hydrophilic group, the 2nd position, which is a carbon, in the non-natural pyrimidine to be linked to a hydrogen bond acceptor or a hydrophilic group, and the 1st position in the non-natural pyrimidine to be a carbon or nitrogen, and the group attached to the 1st carbon position in the non-natural pyrimidine to be a pentose or hexose sugar ring, provided that the non-natural pyrimidine nucleoside is not cytidine or deoxycitidine--natural pyrimidine nucleosides.

Krieg et al. teaches an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural purine nucleoside. The compound of Krieg et al. can also be defined as C*pG, wherein C* is a cytidine analog, G is guanosine, and p is an internucleotide linkage--phosphodiester. The oligonucleotide compound taught by Krieg et al. comprises a non-natural pyrimidine, 5-methylcytosine, which comprises the following characteristic: i) the 5th position, which is a carbon, is linked to a hydrophobic group, ii) the 4th position, which is a carbon, is linked to a hydrogen bond donor; iii) the 3rd position is a hydrogen bond acceptor and is a hydrophilic group; iv) the 2nd position, which is a carbon, is linked to a hydrogen bond acceptor and is a hydrophilic group; v) the 1st carbon position a is a nitrogen; and vi) the group attached to the 1st carbon position is a pentose sugar ring. The non-natural pyrimidine nucleoside in the oligonucleotide compound taught by Krieg et al. is not cytidine or deoxycitidine--natural pyrimidine nucleosides.

Therefore, Krieg et al. teaches the instantly claimed invention. Krieg et al. anticipates the claimed invention.

14. Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by Schwartz.

The relevance of the claims is discussed above. Schwartz teaches an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural purine nucleoside. The compound of Schwartz can also be defined as C*pG, wherein

C* is a cytidine analog, G is guanosine, and p is an internucleotide linkage--phosphodiester. The oligonucleotide compound taught by Schwartz comprises a non-natural pyrimidine, 5-halogencytosine, which comprises the following characteristic: i) the 5th position, which is a carbon, is linked to a hydrogen bond acceptor--which is also a hydrophilic group and an electron withdrawing group; ii) the 4th position, which is a carbon, is linked to a hydrogen bond donor; iii) the 3rd position is a hydrogen bond acceptor and is a hydrophilic group; iv) the 2nd position, which is a carbon, is linked to a hydrogen bond acceptor and is a hydrophilic group; v) the 1st position is a nitrogen; and vi) the group attached to the 1st position is a pentose sugar ring. The non-natural pyrimidine nucleoside in the oligonucleotide compound taught by Schwartz is not cytidine or deoxycitidine--natural pyrimidine nucleosides.

Therefore, Schwartz teaches the instantly claimed invention. Schwartz anticipates the claimed invention.

15. Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Zuo et al.

The relevance of claims 1-4 is discussed above. Claim 5 further limits the non-natural pyrimidine base of non-natural pyrimidine nucleoside to a group consisting of 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine, and 4-thiouracil.

Zuo et al. teaches an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural purine nucleoside. The compound of Zuo et al. can also be defined as C*pG, wherein C* is a cytidine analog, G is guanosine, and p is an internucleotide linkage--phosphodiester. The oligonucleotide compound taught by Zuo

et al. comprises a non-natural pyrimidine, 5-hydroxycytosine, which comprises the following characteristic: i) the 5th position, which is a carbon, is linked to a hydrogen bond donor, which is also a hydrophilic group and an electron donating group; ii) the 4th position, which is a carbon, is linked to a hydrogen bond donor; iii) the 3rd carbon position is a hydrogen bond acceptor and is a hydrophilic group; iv) the 2nd and 3rd carbon position is a hydrogen bond acceptor and is a hydrophilic group; v) the 1st position is a nitrogen; and v) the group attached to the 1st position is a pentose sugar ring. The non-natural pyrimidine nucleoside in the oligonucleotide compound taught by Zuo et al. is not cytidine or deoxycitidine--natural pyrimidine nucleosides. Therefore, Zuo et al. teaches the instantly claimed invention. Zuo et al. anticipates the claimed invention.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. in view of Bennett et al.

The relevance of claims 1-6 and Krieg et al. is discussed above.

Claims 7-8 further limits the non-natural pyrimidine nucleoside to comprise non-naturally occurring sugar moiety, wherein the non-naturally occurring sugar moiety is further limited to arabinose.

Krieg et al. teaches an oligonucleotide compound that comprises the following motif, non-natural pyrimidine nucleoside-phophodiester as the internucleotide linker-a natural purine. Krieg et al. does not teach the use of other non-naturally occurring pyrimidine bases. Additionally, Krieg et al. does not teach the use of non-naturally occurring sugar moiety. However, Bennett et al. teaches a comprehensive listing of non-naturally occurring pyrimidine--which includes 5-hydroxymethylcytosine and 4-thiouracil, and non-naturally occurring sugar moiety-which includes arabinose.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the non-natural pyrimidine bases and non-natural sugar moiety with the oligonucleotide compound of Krieg et al. to evaluate the effect of different bases and sugar moieties on the immuno-stimulatory activity of oligonucleotides that comprises the CpG motif.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the non-natural pyrimidine bases and non-natural sugar moiety with the oligonucleotide compound of Krieg et al. because both references teaches antisense oligonucleotides.

Therefore, one of ordinary of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the claimed invention, absent unexpected results to the contrary.

18. Claims 5-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schwartz in view of Bennett et al.

The relevance of the claims and Schwartz is discussed above.

Schwartz teaches an oligonucleotide compound that comprises the following motif, non-natural pyrimidine nucleoside-phophodiester as the internucleotide linker-a natural purine. Schwartz does not teach the use of other non-naturally occurring pyrimidine bases, such as those recited in the claims. Additionally, Schwartz does not teach the use of non-naturally occurring sugar moiety. However, Bennett et al. teaches a comprehensive listing of non-naturally occurring pyrimidine--which includes 5-hydroxymethylcytosine and 4-thiouracil, and non-naturally occurring sugar moiety-which includes arabinose.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the non-natural pyrimidine bases and non-natural sugar moiety with the oligonucleotide compound of Schwartz to evaluate the effect of different bases and sugar moieties on the immuno-stimulatory activity of oligonucleotides that comprises the CpG motif.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the non-natural pyrimidine bases and non-natural sugar moiety with the oligonucleotide compound of Schwartz because both references teaches antisense oligonucleotides.

Therefore, one of ordinary of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the claimed invention, absent unexpected results to the contrary.

19. Claims 7-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zuo et al. in view of Bennett et al.

The relevance of the claims and Zuo et al. is discussed above.

Zuo et al. does not teach the use of non-naturally occurring sugar moiety. However, Bennett et al. teaches a comprehensive listing of non-naturally occurring sugar moiety-which includes arabinose.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the non-natural sugar moiety with the oligonucleotide compound of Zuo et al. to evaluate the effect of different sugar moieties on the immuno-stimulatory activity of oligonucleotides that comprises the CpG motif.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining the non-natural sugar moiety with the oligonucleotide compound of Zuo et al. because both references teaches antisense oligonucleotides.

Therefore, one of ordinary of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of producing the claimed invention, absent unexpected results to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

E.Le

Shanon Foley
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